UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

**MEMORANDUM**

Subject: I.D. Nos.: 062719-EUU, 062719-EUG,062719-EUP-EL. DowElanco/DE-473 Technical and NAF-46 Formulation. Evaluation of Toxicity Data Submitted and Identification of Outstanding Toxicology Data Requirements

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|---|---|
| Tox. Chem. No. | None |
| PC Code No. | 118202 |
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## I. CONCLUSIONS

The existing database supports Registration of the DE-473 Technical (062719-EUU), the NAF-46 0.1030% formulation (062719-EUG), and the EUP on the NAF-46 0.1030% formulation (062719-EUP-EL) for this use pattern. The waiver requests for the acutes on the 0.1030% formulation are also supported.

## II. ACTION REQUESTED

TB-1 received for evaluation the acute and mutagenicity studies on the technical product required to fulfill data requirements for registration of DE-473 Technical and NAF-46 0.1% Formulation for non-food use. In addition, waivers for the acute studies on the 0.1% Formulation were also requested. These data were submitted by Dow Chemical Company.

## III. BACKGROUND and PRODUCT INFORMATION

DE-473 or hexaflumuron is a benzoyl phenylurea, a chitin-synthetase inhibiting insecticide. It disrupts the molting process in insects, which results in death at immature stages. It is reportedly highly active against a wide range of pests, primarily in Lepidopter, Coleoptera, Homoptera and Diptera.

DE-473 is a solid at room temperature, with a very low solubility in water of $2.7 \times 10^{-5}$ g/l. The NAF-46 formulation contains 0.1% a.i. with 99.9% inert ingredients.

The EUPs will allow the Submitter to continue ongoing field research under different conditions. A total of approximately 75 grams of active ingredient will be applied in bait stations throughout 15 states, utilizing a total area of less than 10 acres. Due to the application method in a bait station enclosure, there is expected to be little chance of human and/or environmental exposure to the active ingredient..

## IV. DATA REQUIREMENTS (CFR 158.135) for Non-Food Use 10/25/93

The requirements (CFR 158.135) for Non-Food Use for this chemical, based on the expected exposure scenario are listed on the next page in Table 1.

**Table 1.**

| Test | | Technical | | 0.1% Formulations | |
|---|---|---|---|---|---|
| | | Required | Satisfied | Required | Satisfied |
| 81-1 | Acute Oral Toxicity | Y | Y | Y | Y§ |
| 81-2 | Acute Dermal Toxicity | Y | Y | Y | Y§ |
| 81-3 | Acute Inhalation Toxicity | Y | Y | Y | Y§ |
| 81-4 | Primary Eye Irritation | Y | Y | Y | Y§ |
| 81-5 | Primary Dermal Irritation | Y | Y | Y | Y§ |
| 81-6 | Dermal Sensitization | Y | Y | Y | Y§ |
| 81-7 | Acute Delayed Neurotox. (Hen) | N | - | N | - |
| 82-1 | Oral Subchronic (Rodent) | N[1] | - | N | - |
| 82-1 | Oral Subchronic (Non-Rodent) | N[1] | - | N | - |
| 82-2 | 21-Day Dermal | N[1] | - | N | - |
| 82-3 | 90-Day Dermal | N[1] | - | N | - |
| 82-4 | 90-Day Inhalation | N | - | N | - |
| 82-5 | 90-Day Neurotoxicity (hen) | N | - | N | - |
| 82-6 | 90-Day Neurotoxicity (mammal) | N | - | N | - |
| 83-1 | Chronic Toxicity (Rodent) | N | - | N | - |
| 83-1 | Chronic Toxicity (Non-rodent) | N | - | N | - |
| 83-2 | Oncogenicity (Rat) | N | - | N | - |
| 83-2 | Oncogenicity (Mouse) | N | - | N | - |
| 83-3 | Developmental Toxicity (one species) | N[1] | - | N | - |
| 83-3 | Developmental Toxicity (two species—rodent & non-rodent) | N | - | N | - |
| 83-4 | Reproduction | N | - | N | - |
| 83-5 | Chronic/Oncogenicity | N | - | N | - |
| 84-2 | Mutagenicity—Gene Mutation | Y | Y | N | - |
| 84-2 | Mutagenicity—Structural Chromosomal Aberrations | Y | Y | N | - |
| 84-4 | Mutagenicity—Other Genotoxic Effects | N | N | N | - |
| 85-1 | General Metabolism | N | - | N | - |
| 85-2 | Dermal Penetration | N | - | N | - |
| 86-1 | Domestic Animal Safety | N | - | N | - |
| Special Studies for Ocular Effects | | | | | |
| | Acute Oral (Rat) | N | - | N | - |
| | Subchronic Oral (Rat) | N | - | N | - |
| | Six-month Oral (Dog) | N | - | N | - |

Legend Y = yes N = no

§ Satisfied by the data on the Technical.

[1] Not Required at this time for these actions because of very low human exposure.

## V. TOXICITY PROFILE

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### A. ACUTE TOXICITY

The Acute toxicity data on DE-473 Technical is summarized below in Table 2. Individual DERs are attached.

TABLE 2. SUMMARY OF ACUTE TOXICITY OF DE-473

| TEST | RESULTS | CATEGORY |
|---|---|---|
| 81-1<br>Acute Oral Toxicity—Rats<br>Study No.: DR-0210-2650-004A<br>Date: January 21, 1993<br>MRID No.:426485-14 | LD50: >5000 mg/kg (Limit Test)<br>Study is Acceptable<br>Toxic Signs: Urine and fecal perineal staining. | IV |
| 81-2<br>Acute Dermal Toxicity—Rabbit<br>Study No.: DR-0210-2650-004D<br>Date: January 21, 1993<br>MRID No.:426485-15 | LD50: >2000 mg/kg (Limit Test)<br>Study is Acceptable<br>Toxic Signs: Local scaling and erythema | III |
| 81-3<br>Acute Inhalation Toxicity—Rat<br>Study No.: DR-0210-2650-005<br>Date: January 21, 1993<br>MRID No.:426485-16 | LC50: ♂ & ♀: >7.0 mg/l<br>Study is Acceptable<br>Toxic Signs: None significant. | IV |
| 81-4<br>Primary Eye Irritation—Rabbit<br>Study No.: DR-0210-2650-004C<br>Date: January 21, 1993<br>MRID No.:426485-17 | Primary Irritation Index: 0.0<br>Study is Acceptable<br>Toxic Signs: Slight redness and chemosis of conjunctivae, resolved within 24 hours. | IV |
| 81-5<br>Primary Dermal Irritation—Rabbit<br>Study No.: DR-0210-2650-004B<br>Date: January 21, 1993<br>MRID No.:426485-18 | PIS: 0.04 (slightly-irritating)<br>Study is Acceptable<br>Toxic Signs: Slight erythema at 72 hr. Resolved in 7 days. | IV |
| 81-6<br>Dermal Sensitization—Guinea Pig<br>Study No.: DR-0210-2650-004E<br>Date: January 21, 1993<br>MRID No.:426485-19 | Not a Sensitizer<br>Study is Acceptable<br>Toxic Signs: None except in positive controls | - - |

## B. SUBCHRONIC TOXICITY

Because of the very limited human exposure expected from the requested use of DE-473, subchronic toxicity testing is not required. However, other requests with different exposure patterns would have to be addressed separately.

## C. DEVELOPMENTAL TOXICITY

Because of the very limited human exposure expected from the requested use of DE-473, developmental toxicity testing is not required. However, other requests with different exposure patterns would have to be addressed separately.

## D. MUTAGENICITY

Four mutagenicity studies are available. They are summarized on Table 3 below. (DERs attached) Data requirements for these FIFRA TOX. Guidelines are satisfied by these submissions; no further studies need be submitted at this time.

**TABLE 3.** MUTAGENICITY STUDIES CONDUCTED DE-473

| STUDY/ LAB/ STUDY # / DATE | MRID | RESULTS | CORE GRADE |
|---|---|---|---|
| Ames Test<br>Hazleton Labs<br>Study # 15138-0-420R<br>10/12/92 | 426485-23 | Negative for reverse mutation in Salmonella TA strains exposed with/without activation up to 5000 μg/plate | Acceptable |
| Gene Mutation<br>Mammalian Cells<br>Hazleton Labs<br>Study # 15138-0-435DR<br>11/04/92 | 426485-22 | Negative for forward mutation at the HGPRT locus of CHO cells exposed with/without activation up to precipitating concentrations (150 μg/ml) | Acceptable |
| Chromosomal Aberrations<br>In Vivo (Mouse MT)<br>Dow Chemical Corp.<br>Study # 2650-003<br>09/10/92 | 426485-24 | Reported negative for inducing micronuclei in PCE of mice treated orally with single doses up to 5000 mg/kg | Acceptable |

| STUDY/ LAB/ STUDY # / DATE | MRID | RESULTS | CORE GRADE |
|---|---|---|---|
| Chromosome Damage<br>In Vitro (Rat Lymphocytes)<br>Hazleton Labs<br>Study # 15138-0-444<br>11/04/92 | 426485-21 | Negative for chromosomal aberrations in rat lymphocyte cultures exposed with/without activation to cytotoxic or precipitating concentrations (100 µg/ml and above) | Acceptable |

## VI. DATA GAPS

There are no data gaps at this time.

## VII. REFERENCE DOSE

An RfD has not been established at this time.

## VIII. OTHER TOXICOLOGICAL CONSIDERATIONS

### A. WAIVER REQUESTS

It is recommended that the waiver request on the 0.1% formulation concerning the required acute studies (81-1 through 81-6) be granted because:

| | |
|---|---|
| Low Toxicity | The Toxicity Category of the Acutes (TG AI) are IV at the Limit Dose, with the exception of Dermal Irritation, which had a Tox. Category of III at the Limit Dose.<br>Based on the Confidential Statement of Formula there is no reason to believe the inerts would be more toxic than the Technical. |
| Low Exposure | The formulation is not water soluble and is contained in the bait matrix in the soil, with no exposure, drift leach or runoff potential. |

It is further recommended that the waiver request on the 0.1% formulation concerning the delayed neurotoxicity study (81-7) be granted, because the structure of the active ingredient does not raise concern for this endpoint.

### B. OECD DATA SUMMARIES

In a separate document (MRID 426485-20), data on studies conducted using DE-473 technical were summarized as follows:

1. DE-473 was not oncogenic in Sprague-Dawley rats at dietary dose levels up to

500 mg/kg/d for 104 weeks. While no gross or clinical signs were noted, an increased incidence and severity of liver pale cell foci were observed at 500 mg/kg/d. the NOEL was 75 mg/kg/d.

2. DE-473 was not oncogenic in CD-1 mice during 80 weeks of treatment at dietary levels up to 25 mg/kg. No other toxic effects were noted.

3. In beagle dogs the target organ was peripheral blood cells. The NOEL for the one year feeding study was 0.5 mg/kg/d, with Heinz body formation and reversible increases in methemoglobin observed at 5 and 25 mg/kg/day.

4. DE-473 was not developmentally toxic in rats or rabbits at oral dose levels up to 1000 mg/kg/day. Furthermore, DE-473 was reported to have no effect on fertility, reproductive performance or fetal development at 125 mg/kg/d, the highest level tested in a two-generation study.

The actual data from these studies were not presented, and these summaries are presented here for general information only.

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